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Tuberculosis and Histoplasmosis Co-Infection in AIDS Patients

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Abstract. Coinfection with tuberculosis in some countries occurs in 8–15% of human immunodeficiency virus (HIV) -infected patients who have histoplasmosis. This coinfection interferes with prompt diagnosis, and treatment is difficult because of drug interactions. We retrospectively reviewed the cases of 14 HIV-infected patients who had concomitant tuberculosis and histoplasmosis. The most frequent clinical manifestations were weight loss (85.7%), asthenia (78.5%), and fever (64.2%). The diagnosis of histoplasmosis was made primarily by histopathology (71.4%), and the diagnosis of tuberculosis was made by means of direct microscopic examination (71.4%). Death occurred in two patients, and relapse of both infections occurred in one patient. Moxifloxacin was substituted for rifampicin in six patients, with good outcomes noted for both infections. The clinical presentation does not readily identify acquired immunodeficiency syndrome (AIDS) patients who have tuberculosis and histoplasmosis. The use of a fluoroquinolone as an alternative agent in place of rifampicin for tuberculosis allows effective therapy with itraconazole for histoplasmosis.

INTRODUCTION

In developing countries, late diagnosis of human immunodeficiency virus (HIV) infection plus the difficulties in procuring access to antiretroviral treatment favor the occurrence of opportunistic infections. Tuberculosis (TB) is the leading opportunistic infection among these patients, with an estimated worldwide incidence of 1.1 million coinfected patients and 350,000 annual deaths.[1] In the HIV-infected population, the incidence of histoplasmosis in endemic areas reaches 5% per year.[2] Both infections converge in Latin America, where histoplasmosis is endemic and TB incidence rates reach as high as 135 per 100,000 persons in some countries.[1]

The occurrence of both TB and histoplasmosis in an HIV-infected patient who is severely immunosuppressed has important implications for diagnosis, treatment, and prognosis. Both opportunistic diseases can produce similar pulmonary, nodal, and miliary involvement. The clinical aspects, basic laboratory tests, and radiological abnormalities often overlap, making specific diagnosis difficult.[3,4] There are significant drug interactions among rifampicin, itraconazole, and antiretroviral therapies, especially when non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) are prescribed. Rifampicin is a potent inducer of cytochrome P450 enzymes, and its prescription results in undetectable itraconazole levels in HIV patients who are receiving these two medications.[5] Rifampicin can also significantly decrease plasma concentrations of NNRTI and PI.[6] Concomitant use of itraconazole and PI may result in increased plasma concentrations of both drugs, especially if ritonavir is used.[6] Simultaneous administration of NNRTI and itraconazole also produces changes in plasma concentrations of both medications; NNRTI levels are increased, and azole levels are decreased.[6]

Limited data are available concerning TB and histoplasmosis coinfections in HIV-infected patients. The work by Huber and others[7] reported a coinfection frequency of 8% in French Guiana, and the work by Gutierrez and others[8] found that 15.4% of 104 patients with disseminated histoplasmosis in Panamá also had coinfection with TB. However, no in-depth description of these patients with dual coinfections was presented in the series mentioned above. A limited number of case reports dealing with problems of diagnosis or treatment has been published previously.[4,9–13] We report our experience with a series of HIV-infected patients who had TB and histoplasmosis coinfection.

PATIENTS AND METHODS

Study design and patients. We conducted a retrospective review of HIV-infected patients who had been diagnosed and treated for both TB and histoplasmosis at the Hospital La María and the Corporación para Investigaciones Biológicas (CIB) in Medellín, Colombia, during the period from January of 1992 to March of 2011. Patients were included if their clinical records had sufficient information on diagnosis and treatment and if they met the definition of coinfection. By consensus among the authors, the diagnosis of TB and histoplasmosis coinfection was considered established when both infections were diagnosed during the same hospital admission, histoplasmosis was diagnosed during the first 2 months of TB treatment, or TB was diagnosed within the first 3 months of treatment of histoplasmosis.

The diagnosis of TB was confirmed by isolation of *Mycobacterium tuberculosis* in culture, observation of acid-fast bacilli (AFB) in smears from respiratory secretions, or tissue histopathology in the absence of growth of other mycobacteria.[14]

Histoplasmosis was considered proven when typical 2–4 μm budding yeasts were observed by direct examination or in tissue sections or when *Histoplasma capsulatum* was isolated in culture.[15]

Definitions. Relapse is defined as the resurgence, after initial resolution, of signs and/or symptoms attributable to at least one of two diseases during the time that the patient was treated for both infections.

Successful therapy is defined as resolution or improvement of signs and symptoms attributable to both infections evaluated at the time of the last visit or at month 12 for those patients who continued follow-up.

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Data management and statistical analysis. Clinical records and microbiological results of the patients included in this study were reviewed to extract the epidemiological, clinical, imaging, and laboratory data required for this report. Data were stored in a database constructed for this purpose. A descriptive analysis was done using absolute frequencies with percentages to present qualitative data and mean with SD for quantitative data.

Ethical considerations. This research was conducted in accordance with the parameters established by the Ethics Committee of the CIB and the principles of Declaration of Helsinki for research in humans. Because of the retrospective design of this study, a signed informed consent was not required.

RESULTS

In the 19 years from January of 1992 to March of 2011, 30 HIV-infected patients were diagnosed as having both TB and histoplasmosis at the CIB and treated for both diseases at the Hospital La María; 14 of 30 patients (46.7%) met the criteria for inclusion in the study. Ten patients were excluded, because their coinfection criteria could not be ascertained, and another six patients were excluded because of insufficient data on diagnosis and treatment; 12 of 14 (85.7%) patients included in the review were men. The course of their HIV infection was estimated to be a median (interquartile range [IQR]) of 28.5 (81) months, and 71.5% were naïve to antiretroviral therapy. The median (IQR) CD4 count was 70 (102) cells/μL, and HIV viral load was 231,000 (306,000) copies/mL (Table 1).

The most frequent complaints of the coinfected patients were constitutional symptoms. The air-borne route of infection occurs in both TB and histoplasmosis, but respiratory symptoms were noticed in less than one-half of the patients. However, pulmonary infiltrates were observed in 11 (78.5%) patients. Involvement of the lymph nodes occurred in 11 patients, hepatomegaly occurred in 9 patients, and splenomegaly occurred in 7 patients. Laboratory tests revealed anemia (median hemoglobin = 10 g/dL, IQR = 3.4 g/dL), increased lactate dehydrogenase (LDH) in five of six patients evaluated (median = 625 IU/L, IQR = 550 IU/L), and increased alkaline phosphatase (median = 217 IU/L, IQR = 174 IU/L). The median leukocyte count was 4,500 cells/μL (IQR = 2,800 cells/μL), and the median platelet count was 212,000/μL (IQR = 183,750/μL) (Table 2).

The diagnosis of histoplasmosis was made by culture in six patients (42.8%); histopathological examination yielded the diagnosis in 10 patients (71.4%). *H. capsulatum* was identified by culture or histopathology in lymph nodes in seven patients, bronchoalveolar lavage (BAL) or lung biopsy in five patients, skin, gastrointestinal tract, or liver biopsy in two patients each, and bone marrow in one patient. In five patients, *H. capsulatum* was identified in more than one organ.

In 10 patients (71.4%), AFB were observed in smears, and growth of *M. tuberculosis* was obtained in eight (57.1%) of the cases (Table 3). AFB were observed or *M. tuberculosis* was isolated from respiratory samples (BAL, sputum, or lung biopsy) in 12 patients, lymph node biopsies in 6 patients, urine or gastrointestinal tract biopsy in 2 patients each, and skin biopsy, bone marrow, and blood in one patient each. In eight patients, AFB were found in more than one organ.

In 12 patients, the diagnosis of both infections was made during the same hospitalization. In the remaining two patients, the diagnosis of histoplasmosis was made during the first 2 months of treatment of TB.

In 10 (71.4%) patients, histoplasmosis was treated with amphotericin B deoxycholate as induction therapy (median cumulative dose = 562 mg, IQR = 162.5 mg). After a clinical response was seen, therapy was changed to itraconazole (600 mg daily loading dose for 3 days and then 400 mg daily). Four patients received only itraconazole therapy. Intensive-phase

TABLE 1

Baseline data of 14 HIV-infected patients with both histoplasmosis and TB coinfection

Variable	Measurement
Male sex (%)	12 (85.7)
Median age (years; IQR)	36.5 (10)
Median time living with HIV (months; IQR)	28.5 (81)
HIV diagnosis made at the time of coinfection (%)	4 (28.6)
Median CD4 count (cells/μL; IQR)	70 (102)
Median viral load (copies/mL; IQR)	231,393 (306,214)
Other opportunistic infection* (%)	4 (28.5)
Antiretroviral use (%)	4 (28.5)
Median days of symptoms before diagnosis (IQR)	45 (100)

*Cryptococcosis, *Pneumocystis jirovecii* pneumonia, cytomegalovirus retinitis, *M. genavense* infection, Toxoplasma encephalitis, or hepatitis B.

TABLE 2

Clinical presentation of 14 HIV-infected patients with histoplasmosis and TB coinfection

Symptoms	Number (%)	Findings	Number (%)
Weight loss	12 (85.7)	Anemia (female < 12 g/dL, male < 13 g/dL)	12 (85.7)
Asthenia	11 (78.5)	Increased LDH (> 221 U/L)	5/6 (83.3)
Fever	9 (64.2)	Lymphadenopathy	11 (78.5)
Anorexia	8 (57.1)	Lung infiltrates*	11 (78.5)
Cough	7 (50)	Increased ALP (> 96 U/L)	10/13 (76.9)
Expectoration	6 (42.8)	Hepatomegaly†	9/13 (69.2)
Abdominal pain	6 (42.8)	Splenomegaly†	7/13 (53.8)
Dyspnea	5 (35.7)	Increased AST (> 40 U/L)	6/13 (46.1)
Diaphoresis	4 (28.5)	Leukopenia (< 4,500 cells/mL)	6 (42.8)
Chest pain	4 (28.5)	Mucocutaneous lesions	6 (42.8)
Behavioral disturbances	3 (21.4)	Increased ALT (> 40 U/L)	5/13 (38.4)
Diarrhea	3 (21.4)	Thrombocytopenia (< 150,000)	4 (28.5)
Vomiting	3 (21.4)	Lung calcifications*	3 (21.4)
Headache	2 (14.2)	Ascites†	2/13 (15.3)
		Lung nodules*	1 (7.1)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
*Findings on chest X-ray.
†Findings on abdominal ultrasound.

TABLE 3

Method of diagnosis in 14 HIV-infected patients with histoplasmosis and TB coinfection

Method	Histoplasmosis* (%)	TB* (%)
Culture	6 (42.8)	8 (57.1)
Direct examination	5 (35.7)	10 (71.4)
Histopathology	10 (71.4)	7 (50)

*Percentages may add up to more than 100%, because more than one diagnostic test often was positive in the same patient.

TABLE 4
Outcome of 14 HIV-infected patients with histoplasmosis and TB coinfection

Outcome	Number (%)
Death	2 (14.3)
Relapse	1 (7.1)
Successful therapy	9 (64.3)
Improvement	4 (44.4)
Resolution	5 (55.6)
Lost to follow-up	2 (14.3)

treatment of TB was isoniazid, ethambutol, and pyrazinamide with either rifampicin (10 patients) or moxifloxacin (4 patients). Two patients treated initially with rifampicin were later switched to moxifloxacin, and another patient was switched to ciprofloxacin; 11 of 14 patients were followed after hospital discharge for a median (IQR) of 7 (10.3) months (Table 4). In the continuation phase of TB therapy, 6 of 11 patients who were followed-up received rifampicin, and 5 patients received a quinolone. Of the remaining three patients, one patient died during hospitalization because of coinfection. This patient had received anti-TB treatment that included rifampicin, and for histoplasmosis, the patient had been treated initially with amphotericin B deoxycholate (400-mg cumulative dose) followed by oral itraconazole. Because of clinical worsening and undetectable serum concentrations of itraconazole, rifampicin was changed to ciprofloxacin without clinical improvement. Amphotericin B and rifampicin were again given, but the patient died of ongoing infection. Two other patients were lost to follow-up after being discharged from the hospital.

One of eleven patients who had follow-up studies died of coinfection at the 8th month of treatment with an anti-TB regimen that included rifampicin; the patient had received amphotericin B initially and then was stepped down to itraconazole therapy. Serum concentrations of itraconazole on three different occasions were < 0.5 μg/mL and thought to be caused by irregular adherence to the antifungal regimen. Another patient relapsed with active TB and histoplasmosis during treatment. He was retreated with rifampicin-based anti-TB therapy and itraconazole but had poor adherence to the antifungal treatment, and serum itraconazole concentrations were undetectable. Of the remaining nine patients, four patients (44.4%) had improvement of signs and symptoms; the remaining five patients (55.6%) achieved clinical resolution at the last follow-up visit (Table 4). Five of the nine patients followed up received induction therapy with amphotericin B deoxycholate; three of the patients showed resolution of clinical manifestations, and the other two patients showed improvement. Of the four patients who received only itraconazole, two patients showed improvement of clinical manifestations, and two patients had resolution at the last visit.

In five patients, serum itraconazole levels were obtained at least one time during treatment. Only two patients, both of whom were receiving anti-TB treatment based on quinolones, had itraconazole levels (1.02 and 2.17 μg/mL); the other three patients were treated with rifampicin and had undetectable levels of this agent (Table 5).

TABLE 5
Treatment, outcomes, and serum itraconazole levels of 12 HIV-infected patients who had histoplasmosis and TB and received itraconazole

Treatment	Number (%)	Itraconazole levels		Outcome
		Level (μg/mL)	Number (%)	
Quinolone and itraconazole	6*	Not done	4	Successful therapy
		> 1.0	1	Successful therapy
		> 1.0	1	Lost to follow-up
Rifampicin and itraconazole	6	Not done	3	Successful therapy
		< 0.5	1	Death
		< 0.5	1	Relapse
		< 0.5	1	Successful therapy

*Three patients started with rifampicin and then changed to quinolone.

DISCUSSION

The presence of multiple opportunistic infections in HIV-infected patients is a frequent event that occurs in up to 33% of cases.[16] In some countries, it is estimated that TB coinfection occurs in 8–15% of HIV-infected patients who have histoplasmosis. The patients with histoplasmosis and TB coinfection described in this series had advanced HIV infection with a median CD4 count of 70 cells/μL, and most of these patients (71%) were naïve to antiretroviral treatment. Thus, they were at great risk for infection with intracellular pathogens, such as TB and histoplasmosis.

From the demographic point of view, the predominance of males (85.7%) in this study was notable, but it coincides with the distribution of acquired immunodeficiency syndrome (AIDS) in Colombian populations; 85% of patients with disseminated histoplasmosis are male, and 92% of patients with TB are male.[17,18]

Dual infection poses serious challenges for diagnosis and treatment. TB and histoplasmosis share several signs and symptoms, including fever, fatigue, night sweats, lymphadenopathy, and hepatosplenomegaly.[12] Development of adrenal insufficiency can occur with both TB and histoplasmosis, but it is more commonly described with disseminated histoplasmosis.[19] Skin lesions also seem to be more common with disseminated histoplasmosis than with TB and provide easy access for diagnostic biopsy.[20,21]

It was interesting to observe that, despite the fact that both TB and histoplasmosis are airborne diseases, the corresponding pulmonary complaints were absent in one-half of the patients. Nonetheless, X-rays revealed infiltrates in 78.5% of the cases, thus revealing a dichotomy between clinical findings and imaging studies. Both diseases were clearly systemic, which was indicated by overt involvement of liver, spleen, and lymph nodes in a high proportion of patients, although it could not be ascertained whether one or both of the infections caused the abnormalities.

In regard to laboratory studies, pancytopenia and increased liver enzyme tests are commonly noted with both infections; elevated acute phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and serum ferritin, are also common to both illnesses, although markedly elevated serum ferritin levels might be more suggestive of histoplasmosis.[22] Clearly, when biopsy material is available, it is important to look for both fungal and acid-fast organisms. Histopathological evaluation provided the most efficient means for establishing the diagnosis of histoplasmosis.

When both infections occur simultaneously, the diagnosis of TB should be considered first, because this disease is more common, and it is important to prevent the spread of infection to others. The diagnosis of histoplasmosis is usually thought of later when the patient shows no improvement with antituberculosis agents.[4,12,13]

More than 60% of our patients responded to treatment, but two patients died and one patient relapsed, all because of treatment failure. In these three patients, it was likely that the interaction between itraconazole and rifampicin that resulted in undetectable azole levels contributed to treatment failure. Additionally, two of these patients had low adherence to itraconazole dosing. Interactions between itraconazole and rifampicin are well-known. The work by Jaruratanasirikul and Sriwiriyajan[5] showed this interaction in a group of healthy individuals and patients with HIV who had undetectable serum itraconazole levels when rifampicin was given. Failures of itraconazole therapy in AIDS patients who had coinfection with histoplasmosis and TB have been reported.[4,9–11]

There are several treatment alternatives that could perhaps obviate this drug–drug interaction, but most are not acceptable. For example, rifabutin could be used in place of rifampicin, but it also decreases the serum concentration of itraconazole[23] and is not available in many of the countries in which these infections occur. Amphotericin B could be used in place of itraconazole, but there are obvious concerns about adverse events and the need for parenteral administration. Posaconazole has fewer cytochrome P450 interactions than other azoles and is an attractive alternative, but experience with this triazole for treating histoplasmosis is limited.[24] In addition, there have been reports of decreased serum levels of posaconazole and clinical failure when used concomitantly with rifampicin.[25]

An option that may prove superior to any of the above options is to replace rifampicin with moxifloxacin. This option is the alternative treatment that we pursued, and we found no failures in the small number of patients who were treated in this manner. Fluoroquinolones have had a role in the treatment of TB for some time. Currently, fluoroquinolones, especially moxifloxacin, are the cornerstone of treatment of multidrug-resistant and extensively drug-resistant TB.[26,27] In recent years, the role of fluoroquinolones in the treatment of susceptible TB as a means to shorten the duration or therapy has been explored. A greater rate of negative cultures by week 8 was shown when moxifloxacin-based therapy was compared with standard therapy.[28,29] However, these studies evaluated the use of moxifloxacin in place of drugs other than rifampicin, the agent with the highest number of drug–drug interactions. A fluoroquinolone is recommended to replace the rifampicin in cases of infections caused by strains resistant to the latter, but according to current recommendations, treatment with a regimen without rifampicin should be extended for as long as 12–18 months.[30]

In conclusion, the clinical presentation does not allow us to readily identify those AIDS patients who are infected with both histoplasmosis and TB. Thus, clinical suspicion must be high for dual infection, especially in patients whose disease course is unsatisfactory. It is important to look for alternative therapies when dual infection is present because of the significant drug–drug interactions between rifampicin and itraconazole. In our patients, moxifloxacin seemed to be effective in the treatment of TB and did not interact with itraconazole, allowing a satisfactory response to therapy for histoplasmosis. However, the number of patients treated in this manner is small, and clearly, more studies should be done to ascertain the value of this fluoroquinolone.

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